REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1, 5, 7-14, 16-17 and 24-31 are pending. The title is amended to be more descriptive of the claimed invention.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1, 5 and 9-11 were rejected under Section 102(b) as allegedly anticipated by Suzuki et al. (J. Appl. Physiol. 81:1213-1222, 1996). Applicants traverse. The Examiner's consideration of the previously submitted Mian Declarations is requested.

Applicants' claimed method is believed to be the first physiologically-relevant test for objectively testing (i.e., quantitative measurements of superoxide production) for an effect of psychological stress. It is performed as a simple whole blood test. Hence, there is commercial interest in diverse fields from animal handling to car design, and related to various occupations recognized as having the potential to create psychological stress (e.g., service in the armed forces). A key point for the ease and physiological relevance of Applicants' claimed invention is that it is a whole blood test that measures chemically-induced superoxide production. By contrast, Suzuki discloses no method that processes test and control samples comprised of whole blood.

Suzuki discloses two methods. The first is a histochemical staining test directed at enumerating activated neutrophils in peripheral blood smears using nitro blue tetrazolium (NBT). The total number of neutrophils, including those stained by NBT (i.e., NBT-positive) or not (i.e., NBT-negative), were counted in Table 4 and Fig. 3. But there is no result that determines superoxide production in test and control samples comprising whole blood. Moreover, no increased superoxide production over basal was measured. For example, the NBT score in Table 4 is not a determination of superoxide production

using PMA as chemical inducer because the test sample would be 738.0 (= 758.2 – 20.2) and the control sample would be 734.2 (= 759.6 – 25.4). Thus, there is no **lower** increased chemically-induced superoxide production over basal in the test sample (738.0) compared to increased chemically-induced superoxide production above basal in the control sample (734.2) as required by Applicants' present invention.

The second is a chemiluminescent test performed on neutrophils isolated from peripheral blood. Thus, the results shown in Table 5 also fail to satisfy the requirements of Applicants' claimed methods, which exclude a separation step. Hence, samples can be quickly processed in the present invention. Applicants' claimed method relies on a very different inventive concept than Suzuki's tests. The present invention leaves cells in contact with naturally circulating stress hormones and other soluble immune mediators, all of which can modulate superoxide production by the unseparated blood cells in a test or control sample, and the cells can be rapidly processed without a significant change in reactivity. This is also reflected in the very different results obtained by Suzuki and the claimed methods. Table 5 fails to determine basal superoxide production (i.e., a test or control sample not stimulated with OZ). Moreover, Suzuki found that lucigenin detection of superoxide production by isolated neutrophils stimulated with opsonized zymosan was decreased slightly for test samples; the difference is not significant. Changing the probe to luminol resulted in superoxide production that was significantly higher. By contrast, Applicants' present invention gives a **lower** increase in chemically-induced superoxide production over basal in test samples from an individual exposed to a psychological stressor. Suzuki fails to mention coping capacity at all. And PMA and FMLP were not used as chemical inducer in Suzuki's chemiluminescent test.

Therefore, histochemical and chemiluminescence assays following an exercise regime (i.e., Suzuki) are simply not comparable to Applicants' present invention. Neither the measurement of stress effect nor coping capacity is anticipated by Suzuki. Applicants' process ensures that in vitro results are indicative of the in vivo physiological situation. It can be performed quickly using little processing because whole blood can be used as the test and control samples. Increased superoxide production above basal (i.e., difference between presence and absence of chemical inducer) in a test sample is

compared with increased superoxide production above basal (i.e., difference between presence and absence of chemical inducer) in a control sample. A lower increase in the test sample as compared to the control sample indicates exposure to psychological stress, and coping capacity is the residual capacity to increase superoxide production above basal in the test sample.

Therefore, Suzuki does not disclose Applicants' method according to claim 1. In particular, there is no assay disclosed in the cited document that measures superoxide production with or without the chemical inducer PMA in a whole blood sample; the test sample exposed to psychological stressor and the control sample not being exposed. Suzuki's tests provide no information to the skilled artisan that are relevant to measurement of superoxide production in whole blood samples, inducing superoxide production with PMA, determining the increase in superoxide production over basal, and comparing increased superoxide production over basal between test and control samples to quantify stress effect and coping capacity.

Since Suzuki does not anticipate Applicants' claimed method, claims depending from claim 1 are also not anticipated by the document because all limitations of the independent claim are incorporated in claims depending therefrom. See *In re McCarn*, 101 USPQ 411, 413 (C.C.P.A. 1954).

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge

possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 7-8 and 24 were rejected under Section 103(a) as allegedly unpatentable over Suzuki et al. (J. Appl. Physiol. 81:1213-1222, 1996). Applicants traverse because, as explained above, the cited document fails to anticipate the present claim 1. None of the deficiencies noted above were addressed in the obviousness rejection.

Furthermore, Suzuki teaches against Applicants' claimed methods. As previously explained, the two tests disclosed in Suzuki did not result in lower increased chemically-induced superoxide production over basal in the test sample compared to increased chemically-induced superoxide production above basal in the control sample. The Office Action does not address how this result could be obtained by modifying Suzuki's tests without rendering them inoperable for their intended purposes. Since a modification of the prior art cannot render it inoperable for its intended purpose, the cited document would effectively teach away from the proposed modification and fail to establish a prima facie case of obviousness. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Therefore, Suzuki cannot be relied upon to establish a case of prima facie obviousness.

Claims 12-14 and 16-17 were rejected under Section 103(a) as allegedly unpatentable over Suzuki et al. (J. Appl. Physiol. 81:1213-1222, 1996) in view of Carlson et al. (U.S. Patent 6,319,953). Applicants traverse.

The failure of Suzuki to disclose the claimed invention is not remedied by the attempt to combine that disclosure with Carlson, which discloses a method of screening for stress-relieving drugs. The fundamental deficiencies of Suzuki remain as discussed above. They are not cured by Carlson's disclosure of an irrelevant animal model for drug screening. When test and control samples are taken, how they are processed, and more importantly the comparisons made to indicate a stress effect or to quantify coping capacity were not taught or made obvious by the cited documents. Applicants submit that these features of their claimed invention are sufficient to distinguish over the cited documents so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Therefore, the present claims are not obvious over the combination of Suzuki and Carlson.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 1, 5, 7-14, 16-17 and 24 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. It was further alleged, "The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because claim 1 as presently amended clarifies the relationship between determining whether a stress effect is experienced (i.e., neutrophils in a test sample obtained from the stressed individual are less able to produce superoxide

after contact with a chemical inducer) and coping capacity (i.e., the residual capacity of those neutrophils in the test sample to increase superoxide production above basal).

Applicants' specification describes on page 2, line 23, to page 3, line 29, that stress is quantified (i.e., comparing increased superoxide production above basal by neutrophils with and without the psychological stressor, wherein stress is indicated when the increase in the test sample is lower than the increase in the control sample). They define residual capacity to increase superoxide production above basal after exposure to psychological stress as "coping capacity" (see also original claim 2). This limitation is not "used in a fashion repugnant to the art" as alleged by the Examiner. If this objection is maintained, Applicants respectfully request that the next Office Action provide evidence of a definition in the art that is contrary to its meaning in the claims.

Withdrawal of the written description rejection is requested because the specification demonstrates that Applicants were in possession of their claimed invention.

35 U.S.C. 112 – Definiteness

Claims 1, 5, 7-14, 16-17 and 24 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

As explained above, "coping capacity" is the residual capacity of neutrophils in a test sample to increase their superoxide production above basal when contacted with a chemical inducer and after experiencing psychological stress. This definition is consistent with the definition set forth at page 3, lines 3-4, of Applicants' specification.

Similarly, the present claim 1 clarifies the nature of the "control" sample and is consistent with page 3, lines 18-23, of Applicants' specification ("neutrophils of the same species in a control sample, which are free or substantially free of stress-induced activation or at least derived from one or more individuals exposed to the same regime minus a factor to be tested as a psychological stressor"). In other words, the increase in superoxide production above basal is compared for neutrophils in test and control samples – the former is from an individual who experienced psychological stress and the latter is from an individual who did not experience such stress.

The limitation "above basal" is clarified as being superoxide production by neutrophils in the absence of a chemical inducer. There is increased superoxide production by neutrophils when contacted by the chemical inducer, regardless whether an individual is exposed to stress (e.g., test sample) or not exposed to stress (e.g., control sample). A lowering in increased superoxide production above basal is a measure of stress effect, whereas residual capacity for increased superoxide production above basal when exposed to stress and contacted with chemical inducer is a measure of coping capacity.

The "same" in vitro conditions are used for determining superoxide production by neutrophils in test and control samples, with the exception that a chemical inducer is present or absent depending on whether chemically-induced superoxide production or basal superoxide production, respectively, is measured.

Other limitations objected to by the Examiner are deleted from claim 1 because they are not required for patentability.

Claim 10 does not recite "the resulting" therein.

In claim 12, a test compound having stress-relieving activity is the desired drug.

Withdrawal of the Section 112, second paragraph, rejection is requested because the pending claims are clear and definite.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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